Infant of Diabetic Mother – Not just Glucose

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Speaker Disclosure

- I have no financial interest in the topic discussed.

- I will not discuss therapies which are not FDA approved.

Learning Points

- Maternal diabetes causes an abnormal intrauterine environment
- Abnormal intrauterine environment may cause malformations and growth problems
- In addition to well-known hypoglycemia, infants of diabetics are at risk for other difficulties, including feeding and neurologic problems.

Historical Aspects

- Symptoms of DM recognized for thousands of years (as early as 1500 BC)
- Until insulin, no effective treatment for childhood DM—caloric restriction to 450 kcal/day could prolong life
- **Frederick Banting and Charles Herbert Best developed insulin in 1921 and 1922—injected pancreatic extracts into a diabetic dog, then into a child dying of ketoacidosis**

Type of Diabetes Mellitus

- Type 1—old term "Juvenile-onset DM"
  - 5-10% of cases of diabetes
  - Onset mostly in childhood (15 to 30% of cases occur after age 30 yr) with autoimmune attack on ß-cell
- Type 2 DM—"Adult Onset"
  - About 90% of cases—insulin resistance and deficiency
  - Onset in adolescence to adulthood
- Gestational DM—5% of pregnancies
  - Abnormal glucose tolerance during pregnancy
  - Higher rates in older women, overweight, minorities

DM and Pregnancy

- Pre-gestational v Gestational DM
  - Pre-gestational
    - Type 1—"Childhood Onset"
    - Type 2—"Adult Onset"
  - Gestational: onset of insulin resistance in pregnancy—assumed to have normal glucose level early in pregnancy

Hyperglycemia Early in Pregnancy

- Hyperglycemia ➔ Teratogenic
- IDM risk for congenital malformation: 5-6% overall
- Risk if mother requires insulin: 10-12%
- Congenital malformations cause of death in 50% of IDM perinatal deaths

Fetus and Diabetic Pregnancy

- Increased risk for stillbirth—fetal loss after 20 wk
- Perinatal mortality rate: Stillbirths + infant deaths up to 28 days/1000 births
- Prior to discovery of insulin
  - Successful pregnancy was rare
  - Perinatal mortality rate 65% (1909)
  - Maternal death rate almost 30%

Decline in IDM Perinatal Mortality Rate 1920-2000

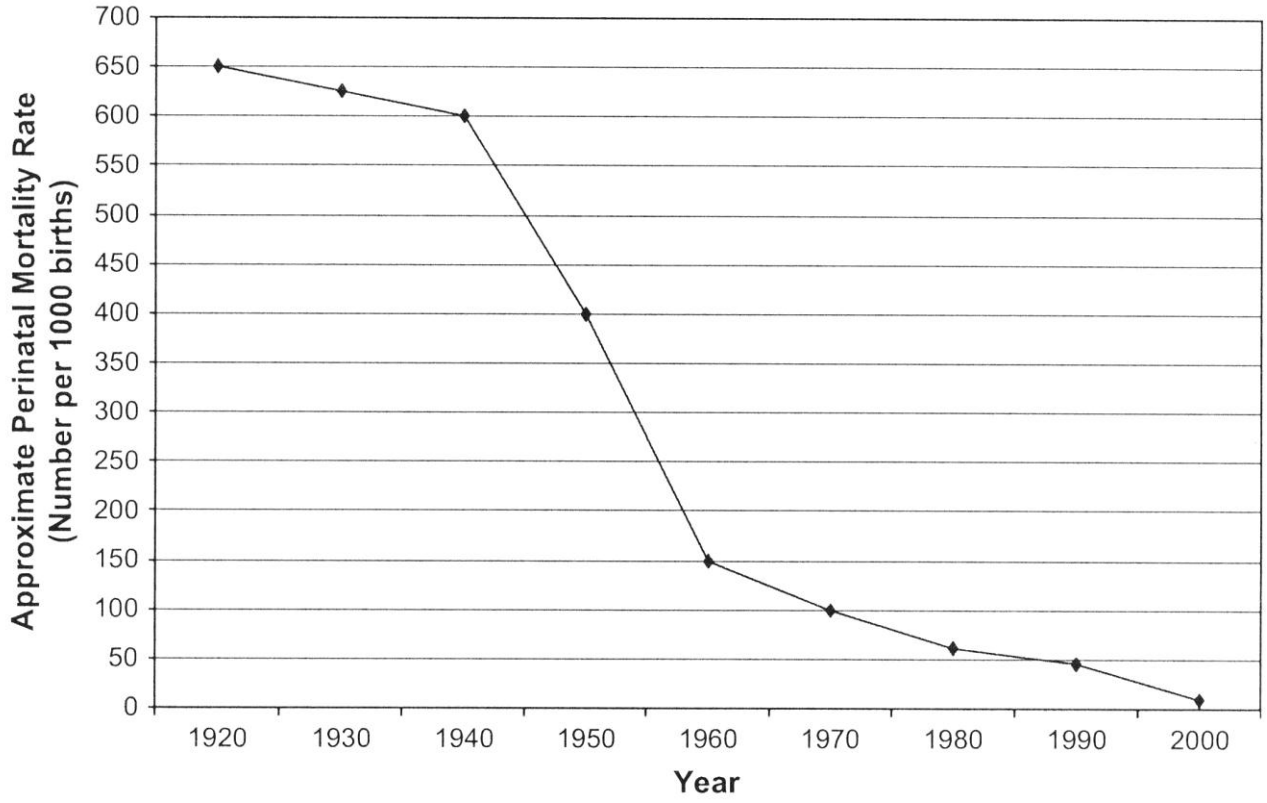


Fig. 1. Estimated rate of stillbirth in diabetic women: 1920–2000. These estimates of the stillbirth rate in diabetic women are based on a summary of the reported literature.

Dudley Clin Perinat 2007

Stillbirth—General Concepts

- National Center for Health Statistics (2003): 6.23/1000 births (overall rate for all pregnancies)
- Rate has been declining for past 50 years
- Most of improvement in rate is for > 28 wks
- Higher stillbirth rates for some groups
  - Non-Hispanic black women: 11.56/1000 births
  - Single women: 8.25/1000
  - Teens, Women > 35 y at higher risk
  - Twins: 16.52/1000
  - Fetal growth restriction with maternal DM

Stillbirth: Type 1 and Type 2 DM

- Type 1:
  - Denmark 1990-2000: 18/1000 pregnancies
  - Denmark 1993-1999: 28/1000 pregnancies (RR 6.2)
  - Scotland 1979-1995: 25/1000 births (RR 4.7)
  - Scotland 1998-1999: 18.5/1000 (RR 3.6)
  - UK 2002-2003: 25.8/1000 births (RR 4.5)
- Type 2:
  - New Zealand (Cundy 2000): 34/1000 v 12/1000 in Type 1—Much worse glucose control in Type 2
  - UK 2002-2003: 29.2 (RR 5.1)

Stillbirth and Gestational DM

- Numbers not as clear as with Type 1 and 2
- Girz (1992): Intensive monitoring
  - 7.7/1000 births
  - Controls: 4.8/1000

- Overall likely some increased risk for stillbirth in GDM, but not to degree of Type 1 or Type 2 DM pregnancies

Causes of Fetal Deaths

- Many cases unexplained
- Fetal hyperglycemia believed to cause acidosis
  - Increased fetal metabolic rate
  - Lactic acidosis (Bradley 1991)
  - Animals: ↑ acidosis and ↑ oxidative damage lead to ↑ fetal deaths and ↑ malformations
- Possibly undetected ketoacidosis (DKA)
  - Perinatal mortality rate 50-90%
- Congenital malformations, infection, vascular insufficiency

Risk for Anomalies (2008 NBDPS study)

- 13,030 infants with anomalies v 4895 controls
  - Risk for Multiple anomalies: highest in mothers with pre-gestational DM (OR 8.62 95% CI 5.27-14.1) — reflects teratogenic effect of hyperglycemia
  - Risk for Single anomaly: higher in pre-gestational DM (OR 3.17 95% CI 2.2 to 4.99)
  - Risk for anomalies ***higher even in those with Gestational DM*** (OR 1.42 and 1.5 for single and multiple anomalies)

Pre-gestational DM and CHD

	Isolated Defect Odd Ratio	Multiple Defect Odds Ratio
Tetralogy of Fallot	4.89 (2.18-10.95)	6.0 (1.67-21.58)
dTGA	3.34 (1.11-10.07)	71.97 (7.43-696
AV Canal	12.36 (3.68-41.49)	25.28 (4.2-152.1)
TAPVR	7.12 (1.99-25.42)	Not estimated
Aortic Stenosis	5.01 (1.09-22.9)	Not estimated
LV Outflow tract problems	4.58 (1.3-16.1)	Not estimated
RV Outflow tract problems	9.61 (3.53-26.15)	9.83 (1.05-91.85)
Perimembranous VSD	2.89 (1.27-6.56)	7.70 (2.37-25.04)
ASD (secundum)	8.47 (4.37-16.42)	13.46 (5.23-34.6)
ASD (unspecified)	5.32 (1.44-19.68)	Not significant
VSD + ASD	5.83 (2.48-13.70)	9.62 (2.95-31.35)
OVERALL	4.64 (2.87-7.51)	10.77 (6.23-18.62)

Congenital Cardiac Malformations

- Overall risk 8.5 per 100 live births to DM
- Defects seen: AV Canals, common atrium, situs inversus, TGA, DORV, VSD, truncus arteriosus, tricuspid atresia, PDA

- Overall incidence of congenital heart disease in all newborns is 1 per 100.

Pre-gestational DM and Other Defects

	Isolated Defect Odds Ratio	Multiple Defect Odds Ratio
All non-cardiac defects	2.34 (1.44-3.81)	7.80 (4.66-13.05)
Anencephaly	3.39 (1.11-10.31)	Not estimated
Spina Bifida	NS	7.99 (1.61-39.70)
Holoprosencephly	NS	16.16 (1.59-163.88)
Anotia/Microtia	3.75 (1.04-13.51)	18.50 (6.95-49.24)
Hydrocephaly	8.8 (3.39-22.84)	12.13 (3.68-39.98)
Cleft Lip ± Palate	2.92 (1.45-5.87)	8.07 (3.05-21.39)
Imperforate Anus	4.70 (1.55-14.26)	8.22 (3.62-18.66)
Biliary Atresia	NS	18.40 (1.84-183.79)
Longitudinal Limb Defic.	6.47 (1.83-22.9)	7.01 (1.91-25.68)
Sacral Agenesis	Not estimated	**130.17 (33.8-501)**

Birth Defects and Gestational DM

- Weaker odds ratios for birth defects seen in gestational DM
  - overall isolated and overall multiple cardiac defects (OR 1.59 and 1.65).
  - Significant for ToF, Pulmonary Stenosis, and Secundum ASDs
- Association of GDM to isolated non-cardiac defects still significant (OR 1.3 (1.05-1.60))
- Why ↑ risk in gestational DM????

Birth Defects in Gestational DM

- Probably a reflection of pre-pregnancy elevation of glucose
- Birth defects seen more often with maternal obesity
- “Gestational DM” in some may actually represent latent Type 2 DM

Effect of Maternal Wt on Defect Risk in DM in Pregnancy (NBDPS)

		OR for Isolated Birth Defect
Pre-gestational	Average Wt	2.61 (1.22-5.58)
	Overweight	3.53 (1.24-10.08)
	Obese	3.92 (2.02-7.62)
Gestational	Average Wt	1.07 (0.78-1.45)
	Overweight	1.90 (1.28-2.82)
	Obese	1.90 (1.38-2.63)

Gestational Diabetics with normal pre-pregnancy wt did not have increased risk for isolated defects.

Risk for multiple defects also showed ↑ risk w/obesitv

Specific Birth Defects

Small Left Colon Syndrome

- Rare
- Bowel obstruction
- Narrow caliber of distal colon beyond splenic flexure
- Usually resolves time
- DDx: Hirshsprung disease

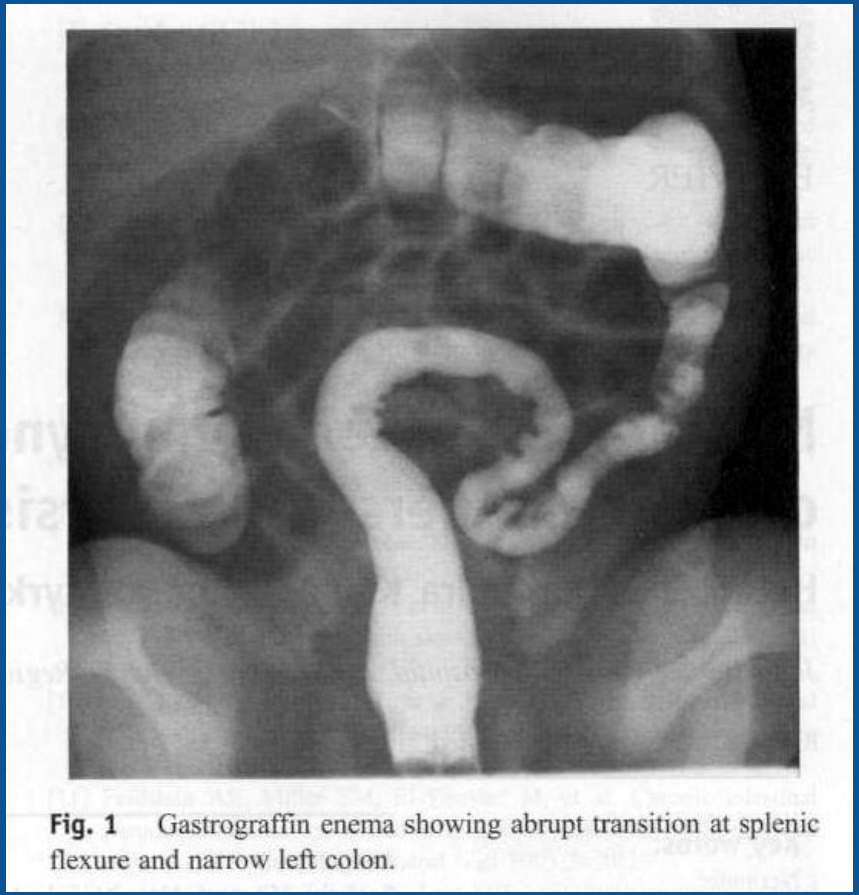
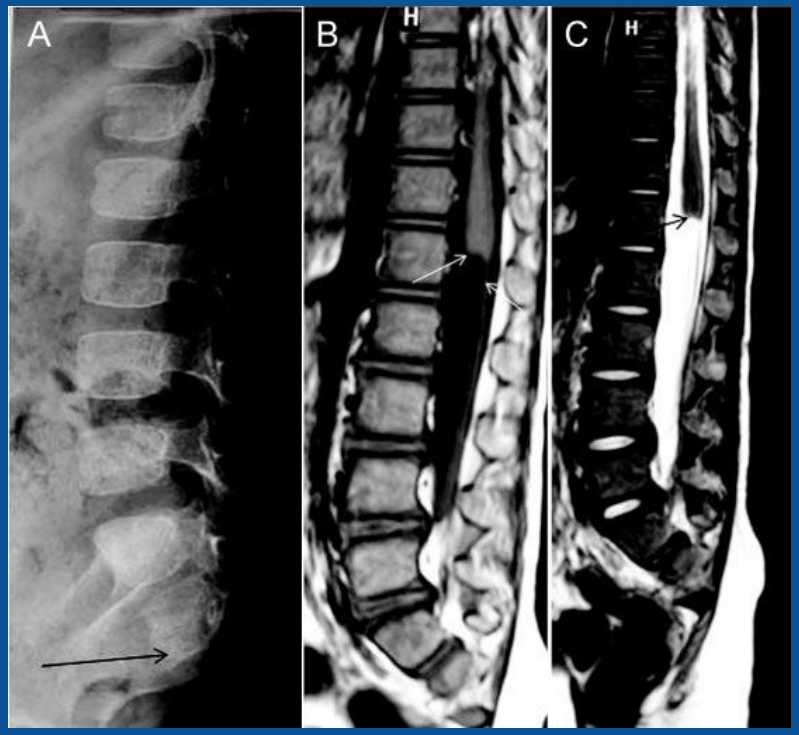


Fig. 1 Gastrograffin enema showing abrupt transition at splenic flexure and narrow left colon.

Ellis et al J Ped Surgery 2009

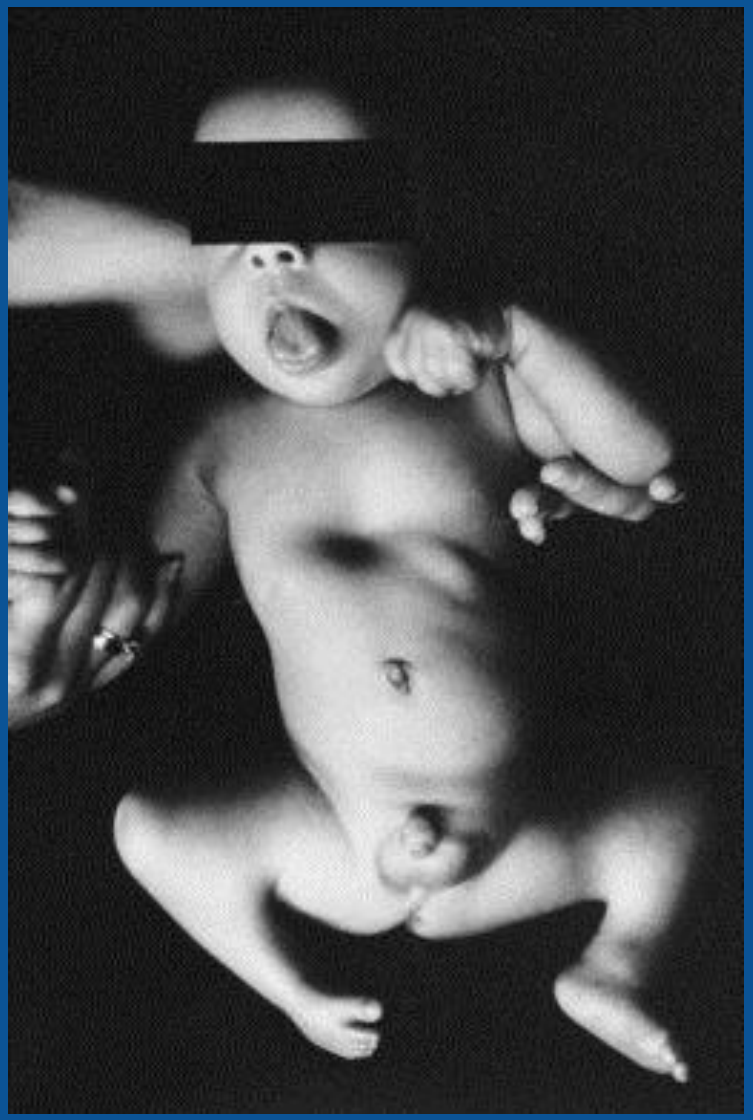
Caudal Regression Syndrome

- Caudal end of spinal cord ends abruptly
- Sacrum hypoplastic
- GU and Lower extremity abnormalities
- Legs may be fused (sirenomelia)
- Rare—but associated with infants of DM



Sharma and Jana, Neurology, 2011

Sacral Agenesis/Caudal Regresion



Gabbe: Obstetrics: Normal and Problem Pregnancies, 6th ed

Macrosomia—"big baby"

- Maternal hyperglycemia→fetal hyperglycemia
- Fetal insulin stimulates growth
  - Hyperplasia and hypertrophy of adipocytes
  - Hypertrophy of organs (liver, heart), skeleton
  - Growth acceleration begins at 25 to 28 wks
  - Brain and renal growth are normal
  - Increased shoulder size due to fat accumulation—risk ↑ shoulder dystocia
  - 50% increase in fat stores compared to controls
- Other substances may also affect growth

Macrosomia – Difficult labor

- Increased shoulder size and abdominal circumference→ more difficult delivery
- ↑ risk for shoulder dystocia
- ↑ risk for injuries (brachial plexus, clavicular fracture, cephalohematoma, phrenic nerve injury, others)
- ↑ risk for asphyxia
  - 27% of 162 infants born to White class B-R-T mothers had signs of asphyxia (nephropathy, prematurity, hyperglycemia before delivery ↑ risk)

But…..they're not always big….

- About 5% of IDMs are IUGR (small)
- Uteroplacental insufficiency
  - Maternal vascular disease (Class F, Class R)
  - Hypertension
  - Protein/Energy malnutrition + hypoxia
  - Need to watch for compromise in delivery

IDM: Polycythemia

- Venous HCT > 65%
  - Mimouni (1993)
    - 29% in IDM
    - 5.9% in controls
- Relative hypoxia in utero from hyperglycemia
- One-third of IDMs had elevated umbilical cord EPO levels
- Direct effects of insulin on RBC precursors may contribute
- Green et al (1992): Maternal Hgb A1C correlated to Neonatal HCT

Polycythemia Evaluation

- Follow venous hematocrit
- Viscosity rises with HCT > 65%
- Monitor for complications of *Hyperviscosity*
  - Hypoglycemia
  - Thrombocytopenia
  - Systemic thrombosis (renal vein, stroke, etc)
  - PPHN
  - Altered neurologic function

Hyperviscosity: Therapy

- Balance risk of therapy with benefit
- IV fluids: low risk, avoids excessive wt loss
- Partial volume exchange transfusion:
  - Sequentially replace blood with Normal Saline to decrease HCT to 55 to 60 range
  - Invasive—requires either UVC, UAC, or peripheral art line
  - Increased risk for necrotising enterocolitis (NEC)
  - Does not improve neurologic outcome

Renal Vein Thrombosis

- Rare, but associated with maternal DM
- Post mortem review of 16 cases
  - 5 were in infants of DM
  - 7 other infants were macrosomic with ß-cell hypertrophy and hyperplasia (very suggestive of fetal hyperinsulinemia)
- Presentation: Hypertension, flank mass, hematuria, thrombocytopenia
- DX: renal doppler US

Altered Iron Stores

- ↑ HCT requires ↑ iron
- Limited Placental transport
- Reduced iron in:
  - Heart: ↓55%
  - Brain: ↓40%
- 65% have low ferritin at birth
- May affect neuro-development (iron deficiency)

- 95% of LGA IDM have altered iron metabolism
  - Low ferritin
  - ↑TIBC
  - ↓Transferrin saturation

- Post-natal iron therapy not clearly beneficial as this is an altered distribution not total body deficiency

Hyperbilirubinemia

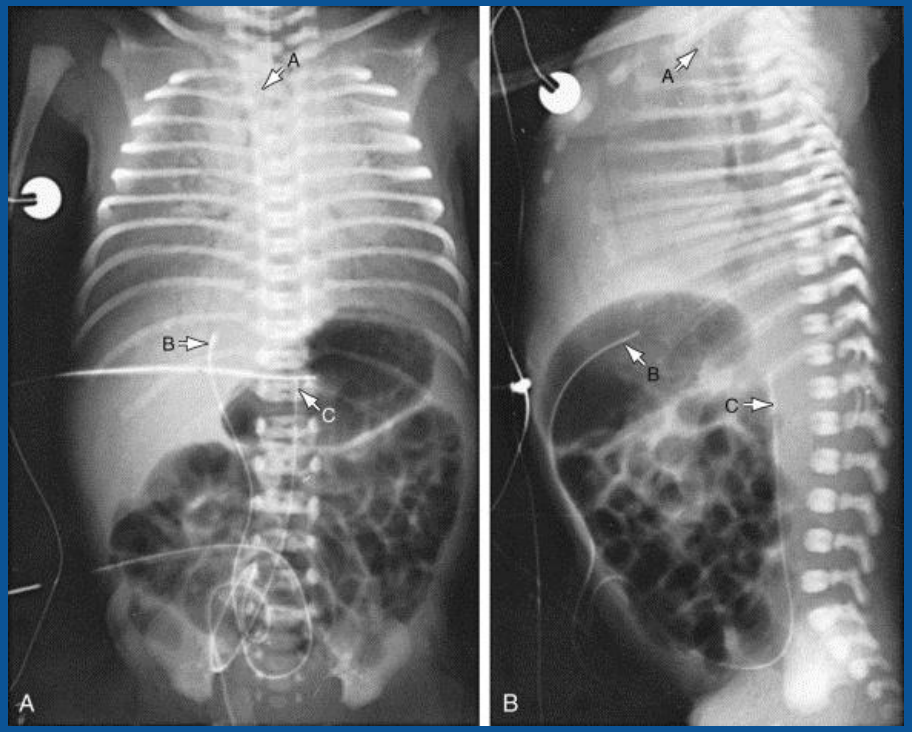
- Jaundice reflects RBC turnover
- ↑ RBC mass in IDM
- Bruising at delivery
- Ineffective erythropoeisis may also contribute
- Phototherapy usually sufficient, but need to be careful regarding bruising and subsequent jaundice

Respiratory Distress Syndrome

- Robert (NEJM, 1976)
  - ↑ risk RDS in IDM
  - RR 5.6 after controlling for confounders
  - Confined to ≤ 38 wk
- Hyperinsulinemia
  - ↓ surfactant due to ↓ substate availability
  - ↓fibroblast-pneumocyte factor activity leads to ↓ Type II pneumocyte activity
- Late preterm infants seem at high risk
- Good maternal control, Modern OB methods ↓ risk

RDS: Clinical Features

- Hypoxia due to diffuse microatelectasis
- Retractions
- Grunting and flaring
- DDx: TTN, pneumonia, sepsis, TAPVR
- Mostly in infants < 39 wk



Kliegman: Nelson Textbook of Pediatrics, 19th ed

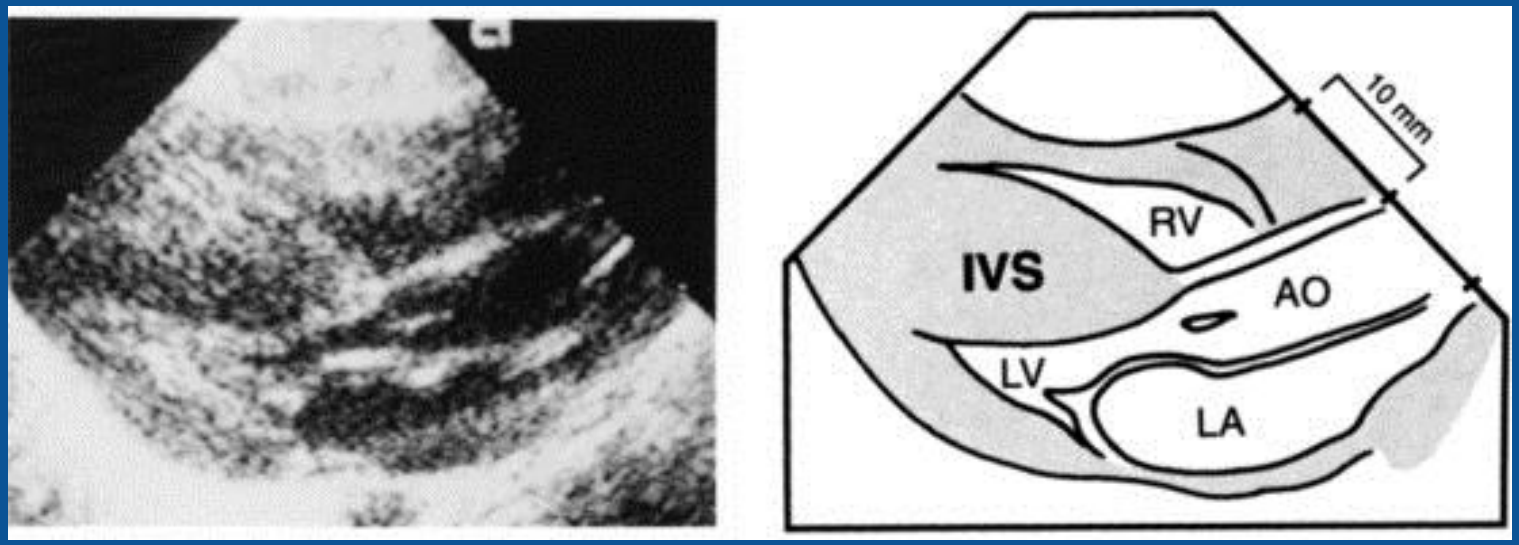
RDS: Therapy

- Stabilize lung volumes with CPAP
- Intubation and surfactant often required
- Watch for Pneumos!!!
  - Needle aspiration
  - Chest tube
  - Incidence higher with CPAP than ETT/Surfactant

Myocardial Hypertrophy

- Myocyte glycogen ↑
- Septal hypertrophy
- Can be obstructive but is usually temporary
- Avoid hypovolemia, pressors
- ± cardiomyopathy (? ↓ iron)

Park: Pediatric Cardiology for Practitioners, 5th ed.



Metabolic Problems: Hypocalcemia

- ↓calcium → PTH secretion
  - ↑ bone resorption
  - ↑ Ca absorption from gut
  - ↑ Ca resorption from urine

- Calcium usually falls during first 24h (placenta shut off)
- PTH secretion then ↑ Ca
- DM appears to blunt PTH secretion and neonatal bone turnover

Hypocalcemia: Clinical Symptoms

- Often asymptomatic
- Jitteriness common
- Can prolong QTc
- Less likely
  - Seizures
  - Poor contractility
- Measure total and ionized calcium
- Consider DiGeorge if cardiac defect, abnormal lymphocytes (send FISH or microarray)

Hypocalcemia: Therapy

- Balance Risks/Benefits
- Usually can follow without therapy
- Calcium IV infiltration
  - Severe
  - May require plastic surgery
- Calcium gluconate 100 mg/kg/dose **slowly**
- Central lines preferred
- Oral therapy possible if stable

Hypomagnesemia

- May be as high as 33% of IDMs
- Symptoms similar to hypocalcemia
- Need to fix magnesium to fix the calcium
- Unclear etiology, may be related to maternal hypermagnesemia

Hypomagnesemia: Treatment

- Magnesium Sulfate:
  - 25 to 50 mg/kg/dose IV q4-6h x 3 to 4 doses
  - Max single 2 grams (well below neonatal levels)
  - Enteral: 100-200 mg/kg/dose PO QID

- Cardiac side effects—need to monitor
  - Bradycardia
  - Heart block
  - Hypotension
  - Calcium gluconate is antidote

Hypoglycemia

- Extremely common among infants of diabetics
- Chronic intrauterine hyperglycemia → robust pancreatic insulin secretion by fetus
- Clamping of cord → shut off of glucose
- Continued insulin secretion causes glucose to drop soon after birth
- Therapy: early feeding (may need a bottle)
  - IV support with dextrose (D10, D12.5 via PIV)
  - Glucagon if needed

Glucose Homeostasis in Late-Preterm and Term Infants—AAP Committee on Fetus and Newborn (2011)

- "Current evidence does not support a specific concentration of glucose that can discriminate normal from abnormal or can potentially result in acute or chronic irrerversible neurologic damage." Pediatrics 127:3, March 2011.
- Glucose levels as low as 30 mg/dL are common in first 1 to 2 hr and usually are transient and asymptomatic.
- "No studies have demonstrated harm from a few hours of asymptomatic hypoglycemia during this normal postnatal period…"

Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants

[(LPT) Infants 34 – $36^{6/7}$ weeks and SGA (screen 0-24 hrs); IDM and LGA ≥34 weeks (screen 0-12 hrs)]

Symptomatic and <40 mg/dL ⟶ IV glucose

ASYMPTOMATIC

Birth to 4 hours of age	4 to 24 hours of age
INITIAL FEED WITHIN 1 hour Screen glucose 30 minutes after 1st feed	Continue feeds q 2-3 hours Screen glucose prior to each feed
Initial screen <25 mg/dL	Screen <35 mg/dL
Feed and check in 1 hour	Feed and check in 1 hour
<25 mg/dL ↓ IV glucose*	25–40 mg/dL ↓ Refeed/IV glucose* as needed
<35 mg/dL ↓ IV glucose*	35 – 45 mg/dL ↓ Refeed/IV glucose* as needed

Target glucose screen ≥45 mg/dL prior to routine feeds

* Glucose dose = 200 mg/kg (dextrose 10% at 2 mL/kg) and/or IV infusion at 5–8 mg/kg per min (80–100 mL/kg per d). Achieve plasma glucose level of 40-50 mg/dL.

Symptoms of hypoglycemia include: Irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding.

Committee on Fetus and Newborn Pediatrics
2011;127:575-579

PEDIATRICS®

IV Support of Glucose

- If significantly hypoglycemic: D10W 2 ml/kg bolus followed by constant infusion of D10W at about 80 to 100 ml/kg/day
- May need D12.5 or even higher dextrose
- Central line needed for > D12.5 (PICC or UVC)
- Glucose infusion rate→useful to track
- GIR = $\frac{\%\ \text{Dextrose X Fluid Rate X } 0.167}{\text{Infant Wt}}$

GIR Calculations

- 5 kg Baby
- Stabilized on D10W at 21 ml/hr (100 ml/kg/day)
- GIR = $\frac{10 \times 21 \times 0.167}{5}$ = 7 mg/kg/min
- Knowing the GIR allows adjustment of dextrose concentration to maintain euglycemia while adjusting total fluids

Hypoglycemia tidbits

- Excessive fluid administration can cause fluid overload→hyponatremia→seizures

So…..

- Follow BMP and follow mL/kg/Day of IVF
- If needing to persistently increase IV rate, then increase dextrose concentration and place central line if needed

Glucagon

- Stimulates gluconeogenesis
- Dose: 200 mcg/kg/dose IV push, IM, or SC
- Continuous: 10-20 mcg/kg/***hour***
- Max dose 1 mg (1000 mcg)
- Lasts 2 hours
- Indications:
  - Hypoglycemia refractory to IV infusions
  - No IV access

Feeding Difficulties

- Feeding difficulties are poorly described in literature

- Periods of intrauterine hypoglycemia may cause secretion of glucagon, which slows intestinal motility (other theory behind Small Left Colon Syndrome)

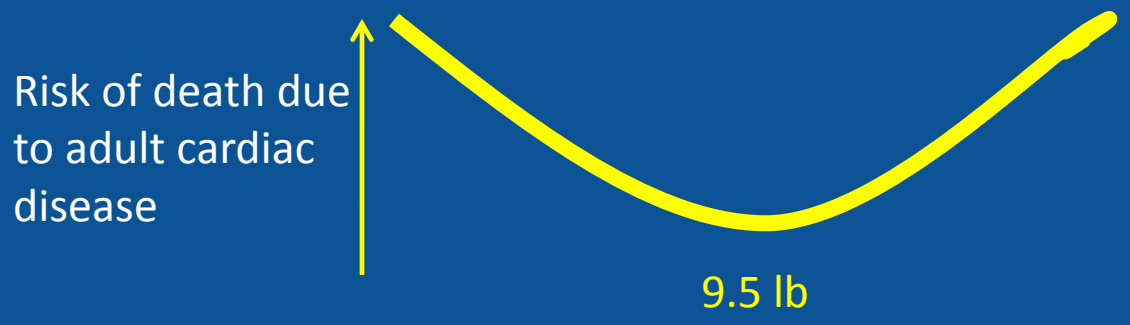
- Late preterm infants of DM may stay in NICU weeks learning to PO feed or be discharged with home gavage feeds (NG or PEG)

Fetal effects: the long term view

- Is adult health influenced by fetal environment???
- Fetal Origins of Adult Diseases
- "Barker Hypothesis"
- Studies in US, UK, and elsewhere in Europe show fetal growth restriction increases risk for adult cardiac disease
- Fetal metabolic "programming" may not adapt well to post natal circumstances

Barker: Infant wt and Adult Cardiac Disease (1993)

- Lower birth weight and wt at 1 year were associated with increased risk for adult death from cardiovascular disease
- Lowest risk was for infants born at 9.5 lbs
- Risk then rose with advancing BW



Fetal Programming

- Hales and Barker (1992) Thrifty Phenotype
  - Fetus adapts to poor intrauterine nutrition by concentrating growth on vital organs (brain)
  - Physiologic response to enhance post-natal survival in environment of questionable nutrition
- Physiologic problems may arise if adaptive response is challenged by abundance of nutrition post natally.
- Concern for excessive post natal growth in growth restricted infants may lead to HTN, insulin resistance, obesity later.

Infant of DM: Uterine Environment

- Intrauterine environment of IDM:
  - Hyperglycemia
  - Chronic increased pancreatic insulin secretion
  - Intermittent hypoglycemia??
  - Increased metabolic rate
  - Increased anabolic rate
  - Increased acidosis
  - Increased growth fat mass, hypertrophy of organs (heart, liver)
  - Increased oxidative stress

Gestational DM: HTN in Offspring

- Mixed results:
  - Jerusalem perinatal study: GDM mothers and > 60,000 singleton offspring at 17 yr→ no association of GDM to hypertension in offspring (born between 1964-1976).
  - Retrospective Pima Indian study showed GDM significantly increased systolic BP in children at 7-11 yr. (Still significant after adjusting for BW and childhood obesity).
  - Third Study (Cho, et al J Pediatrics, 2000) – SBP and MBP was significantly higher in children born to GDM mothers

GDM: Overweight and Obesity in Offspring

- Evidence exists showing GDM is linked to overweight/obesity in offspring:
  - UK study showed
    - ↑ risk for obesity/overweight in 9-11 yo offspring of mothers with GDM, but not Type II DM
    - Higher BMI at 17 yr is significantly associated with GDM
  - Prospective study of over 280,000 Swedish men found maternal GDM during pregnancy was associated with higher BMI at 18 yr.

Type 2 DM in Offspring of DM

- Pima Indian study: Sibling study
  - higher rates of Type 2 DM in those born after mother developed DM (Dabelea, Hanson, et al, Diabetes 2000)

- Pima Indian Study:
  - Offspring of mothers with impaired 3rd trimester glucose tolerance
    - Young adults had ↑ risk (30% at 24 yr) for type 2 DM and risk was directly correlated to degree of hyperglycemia after GTT.
    - If mother had Type 2 DM, 51% risk of type 2 DM for 24 yo offspring.

DM in Offspring of Diabetic Mothers

- Danish Study (Clausen et al Diabetes Care, 2008):
  - Offspring of mothers with DM had 8 fold ↑ risk for diabetes or pre-DM of any type compared to controls
  - Intrauterine hyperglycemia (GDM or Type 1 DM)
    - Increased risk for type 2 DM or pre-DM in offspring
    - At 22 yr, offspring had
      - 21% risk for type 2 DM or pre-DM if mother had GDM
      - 11% risk for type 2 DM or pre-DM if mother had Type 1 DM
      - 4% risk if mother had no DM
  - 3rd Trimester hyperglycemia in Type 1 DM associated risk for diabetes in offspring.

How does this happen??

- Mechanisms unclear—may involve *Epigenetic* modifications

- Epigenetic Modifications are *environmental changes* to gene expression involving DNA methylation, post-translational histone modifications, and other mechanisms that can be passed down between cell generations.

- Interesting field with widespread applications

Infant of Diabetic: Summary

- Watch for congenital anomalies—even if gestational DM
- Often large for gestational age—but may be small if mother has vascular disease
- At risk for hypoglycemia due to insulin secretion "overshooting" cutoff of glucose with clamping of cord
- May also see hypocalcemia, hypomagnesemia, jaundice, polycythemia/hyperviscosity, birth injuries, asphyxia.
- Often feed poorly as neonates.
- Infants of DM appear to be at higher risk for elevated BP, higher weight in late childhood and as adults, and adult DM.